2.D. ***Request for performance testing protocols, effectiveness criteria, and statistical methods employed to analyze data from these tests.***

Procter & Gamble recommends that the Plaque Glycolysis and Regrowth Method (PGRM) should be the only performance test required for marketing stannous fluoride dentifrice, and the PGRM and Disk Retention Assay (DRA) should be the two required performance tests for marketing CPC mouthrinse. (Appendix 1 and Appendix 2)

The Subcommittee recommended that there should be two performance tests that must be passed for a SnF_2 dentifrice to be marketed: (1) *in vitro* determination of the antimicrobial activity of the drug product against representative plaque organisms associated with gingivitis including MIC assays, 30 second kill-time assays, or plaque biofilm assays, and (2) the *ex vivo* Plaque Glycolysis and Regrowth Model (PGRM) which measures biological activity of the finished product. Similarly, the ANPR lists three performance tests for CPC, any *one* of which must be passed for marketing a CPC rinse: (1) *in vitro* microbiological tests, (2) the PGRM, and (3) an *in vitro* Disk Retention Assay. On the basis of available evidence, it is Procter & Gamble's recommendation that the *in vitro* microbiological tests be dropped from consideration as performance tests for SnF_2 and CPC formulations as they do not provide the sensitivity to discriminate between active and inactive final formulations, as do the PGRM and DRA tests. Therefore, we recommend that the PGRM be the only test required for marketing of SnF_2 dentifrices and *both* the PGRM and the DRA tests be required tests for CPC marketing.

Based on the Plaque Subcommittee recommendations for performance testing, Procter & Gamble has optimized the testing procedures to establish the PGRM and DRA tests as performance tests for monograph purposes. The information submitted herein contains the complete description of the method, clinical and statistical protocols, and effectiveness criteria.

Of note, the PGRM test utilizes a comparison to a negative control and a clinically tested positive control. As such, Procter & Gamble has recommended a statistical non-inferiority test to evaluate testing outcomes. The general approach to the non-inferiority test is to demonstrate that a test formulation mean is within a pre-specified range from the positive and negative control means. This statistical recommendation is consistent with the approach described in ICH E9 Statistical Principles for Clinical Trials, Section III.3.2.